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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LUCAS, ZACHARIAH	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 10/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/724,416	JIN ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49 and 51-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49 and 51-69* is/are rejected.

7)☒ Claim(s) *70* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. Currently, claims 49, 51-70 are pending in the application. In the prior action, mailed on January 20, 2004, claims 49-53 were pending and rejected. In the Response filed on July 20, 2004, claims 49, 51, and 52 were amended, claim 50 was cancelled, and claims 54-70 were added to the application.

2. In view of the new rejections raised in this action, the action is made Non-Final.

Priority

3. Applicant's amendment of the application to claim priority to earlier application 08/316,439 is noted.

4. **(Prior Objection- Withdrawn)** The specification was objected to because the reference in the specification to the priority document should indicate the relationship between the applications. In view of the amendment of the application to insert refer to such priority documents in the proper form, the objection is withdrawn.

Information Disclosure Statement

5. The information disclosure statement (IDS) submitted on July 20, 2004 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

Specification

6. **(Prior Objection- Withdrawn)** The specification was objected because it appears to lack proper antecedent basis for the claim language requiring the presence of "an mRNA coding sequence operatively linked to a polymerase binding site of' RSV. In view of the amendment of the Application to insert the required antecedent basis, the objection is withdrawn.

Claim Objections

7. **(New Objection)** Claim 70 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot be dependant on another multiple dependant claim. See MPEP § 608.01(n). Accordingly, the claim has not been further treated on the merits.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. **(Prior Rejection- Withdrawn)** Claims 51-52 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims were rejected because it was not clear what was meant by reference to "key" regulatory or functional domains. In view of the amendment of the claims removing the term "key," the rejection is withdrawn.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. **(Prior Rejection- Maintained)** Claims 49-53 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for immunogenic compositions, does not reasonably provide enablement for anti-RSV vaccines. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The Applicant begins their traversal by stating that the main point of the rejection is that "the art does not presently accept a particular animal model as predictive of human responses to RSV vaccines." The Applicant continues by traversing the rejection on the grounds that the art does accept chimpanzees as such an animal model. The continues by arguing that they have demonstrated efficacy of the claimed virus as vaccines against infection in animals and that, having done so, the identification if virus effective as human vaccines requires no more than routine experimentation. The argument is not found persuasive.

It is first noted that the assertion that there is no accepted model for RSV vaccines was but a part of the overall rejection. The prior action explicitly states that the prior rejection, originally of record in the action of June 5, 2002, is reinstated. This rejection is based not only on the lack of an accepted animal model, but also on the scope of the claims, and the lack of predictability in the art. Thus, each of these issues should be addressed.

The Applicant argues that they have established that the claimed viral particles are both immunogenic, and are able to induce a protective response in chimpanzees. While, as the

Applicant asserts, chimpanzees may be recognized as providing relevant information to those in the art, it does not appear that the teachings in the art support the Applicant's assertion that this animal model is sufficient to demonstrate the effectiveness of an RSV vaccine. A closer reading of the Dudas reference cited by the Applicant shows that the chimpanzee model referred thereto was an experimental model of a particular immunogenically relevant situation. However, as a whole, the art does not support the Applicant's implicit assertion that a showing of effectiveness in this model provides anything more than relevant information relevant to the effect of recombinant RSV in humans. Rather, while the art uses such models to provide information, the art also indicates "the level of attenuation for these viruses can only be determined definitively in human studies." Crowe et al., Virus Res 59: 13-22, at page 20. Thus, the efficacy of a particular virus in chimps does not demonstrate vaccine efficacy in humans.

The Applicant notes that the teachings in the cited Teng reference indicate that "the compositions of the invention" were shown to be effective in chimpanzees. The Applicant then refers attention to MPEP § 2164.02 which states "if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate," to assert that the reference demonstrates that the claimed invention has been enabled. However, in addition to the teachings above that the animal model is not sufficient to demonstrate efficacy of the composition as a vaccine, Teng itself indicates that the showings in chimps do not directly carry over to humans. In particular, on page 9320 of the reference, Teng states that the virus tested in the chimps was both insufficiently attenuated, and overattentuated for the two primary target populations of

human vaccination. Thus, this reference itself both states and demonstrates that the results achieved in chimps do not correlate to the results that would be achieved in humans.

In addition to these teachings, Teng also provides teachings relevant to the predictability of the art of RSV vaccination. Teng teaches that the compositions tested in the reference were not just any attenuated RSV vaccine with any random genetic alteration. The reference teaches that the virus used in the reference was a compilation of several mutations, each of which appears to have been independently identified. Pages 9317, and 9319 (describing the methods of identifying attenuating mutations both through biological means and recombinant experimentation). The reference re-emphasizes the teachings in the art previously cited regarding the difficulty in balancing the attenuation and the immunogenicity of the mutants. Thus, the reference simultaneously teaches that the art involves a good deal of unpredictability, and the identification of effective mutants involves a great deal of experimentation, and that not every virus that falls within the scope of the claims would be capable of providing an effective vaccine against infection.

The teachings of Teng support the Examiners conclusions made from the references cited in the prior action. These references, either individually or cumulatively, demonstrate or describe the unpredictability in the art, and demonstrate that a large amount of experimentation would be required, even with the teachings of the present application, to develop an effective RSV vaccine.

However, the arguments in the Response assert that the problems associated with replicating RNV vaccines have been overcome by the present invention, although there is no illustration of how the problems have been addressed. Further, the claimed invention is drawn to

the use of any genetically mutated attenuated virus. The art, as described above and in the prior actions, clearly teach that not every attenuated RSV would be an effective and safe vaccine. In view of the lack of any evidence that the problems faced in the art have been overcome, and the fact that the claims are broadly enough to include embodiments indicated by the art to be ineffective, it is unclear as to how the claimed invention solves the problems noted in the art.

The Applicant also asserts that the teachings of Prince, cited in the prior action to show that the art recognized no anti-RSV vaccines, are not relevant to the claimed inventions. The Applicant argues that the claimed RSV particles are replicating, while those of primary concern in Prince are not. From this, the Applicant concluded that Prince is not relevant. However, while the body of Prince is concerned with non-replicating anti-RSV compositions, the reference's introduction refers to the failures in, and obstacles faced, with both replicating and non-replicating vaccine compositions. Such generic teachings of problems in the art are clearly indicative of whether the art has resolved the issues.

The Applicant follows the critique of Prince by noting that the teachings of Tang do not affirmatively state that there are no effective anti-RSV vaccines. However, a reading of these references in combination relates the problems being faced in vaccine development and the past failures, and indicates that the search for vaccines continues without citing any effective vaccines that have been found. In view of the summaries of the history of RSV vaccines in these articles, and in other references (such as Crowe et al., Virus Res 59: 13-22, also noting that "Despite over 40 years of vaccine development efforts, an RSV vaccine has not been licensed"), it is clear that the art of RSV vaccination is replete with difficulties and unpredictability. Such teachings

therefore indicate that even if a workable vaccine has been made, it has not yet been recognized as such

In view of these teachings regarding the complexity and unpredictability in the art, and the fact the art does not support a conclusion that one of ordinary skill in the art, upon reading the application, would be able to develop an anti-RSV vaccine without undue experimentation, the Applicant has not enabled the full scope of the claimed inventions.

It is further noted that, even if it is assumed that the Applicant was enabled for a particular embodiment of the claimed viral particles disclosed in the application, the claims are not limited to any such embodiment. Rather, the claims are drawn to vaccine compositions comprising any recombinant RSV comprising a genetic alteration. The art has clearly indicated that not every attenuated RSV virus would be an effective component in anti-RSV vaccines. See, references cited in the prior action. The art also indicates that it would not be immediately obvious to those in the art as to which embodiments would or would not be effective anti-RSV vaccines. In order to practice the claimed inventions to the full extent as claimed, those in the art would have to identify for themselves each other instance where any mutation resulted in a recombinant was both sufficiently attenuated so as not to cause illness or exacerbate illness upon later infection by the live virus, but also sufficiently immunogenic to result in an effective anti-RSV immune response. It is noted that the art indicates that this balance of characteristics is essential for the development of an RSV vaccine. Tang et al., J Virol 77:10819-28, page 10819. In such a case, the claims would remain rejected because the scope of enablement in the present application is not commensurate in scope with the claims. Thus, even if the Applicant's

arguments were found persuasive with reference to specific embodiments, the claims would still be rejected as exceeding the scope of the enabling disclosure.

The Applicant also continues to argue that the Federal Circuit's statement of the test for utility under 35 U.S. 101 in Brooktree v Advanced Micro Devices (24 U.S.P.Q. 2d 1401, 1992) should be applied in the enablement rejection of the present claims. They argue that this is the case because the claims are rejected for inoperability, and that the Federal Circuit decision in In re Brana (34 U.S.P.Q. 2d 1437, 1995) overturned an enablement rejection based on inoperability because the Office had not established that the rejected claims did were not inoperable under the 35 U.S.C. 101 utility standard for inoperability. The Applicant therefore concludes that where the Examiner bases an enablement rejection on inoperability, the appropriate standard for determining the issue is that provided for inoperability under 35 U.S.C. 101. This argument is not found persuasive.

The situation in Brana is not identical to the present application. In this case, the claims have been rejected because the Applicant has not established that those in the art could make or use a vaccine against RSV based on teachings in the application without undue experimentation. The Examiner has not asserted that no attenuated virus could be used as a vaccine, as would be the case in a situation relevant to Brana. Rather, the rejection is based on part on the assertion that the teachings in the art do not support the Applicants argument that efficacy of a virus in protecting a chimpanzee is sufficient to demonstrate efficacy in a human. The Examiner agrees with the Applicant that there is no basis in the art to believe that an attenuated virus would be "totally incapable of achieving a useful result." However, the Examiner does not agree that, based on the teachings of the art and of the application, the Applicant has enabled those in the art

to make and/or use an attenuated RSV as a vaccine against RSV infection. These are separate issues.

As was indicated above, the issue surrounding the animal models of RSV infection is whether those in the art would accept such as demonstrating that a particular attenuated virus would be an effective anti-RSV vaccine. For the reasons provided above, the Examiner has concluded that the art has not established that efficacy in chimps is predictive of efficacy in humans. The Examiner has not concluded that anything is inoperable, but only that the animal model does not demonstrate vaccine efficacy in humans. This conclusion does not, however, rise to the point of questioning the ability of any attenuated virus to act as a vaccine. Rather, this conclusion is merely a factor (state of the art, and/or presence of working examples) considered in determining if the application has provided sufficient information such that those in the art would be able to make or use the claimed RSV variants as a vaccine composition without having to perform undue experimentation.

For these reasons, and the reasons of record, the rejection is maintained.

12. **(New Rejection)** Claims 49, and 51-69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. These claims read on compositions comprising any attenuated RSV comprising a genetic alteration. Dependant claims further identify the genetic alterations as a substitution, addition, or

deletion of one or more nucleotides. The claims are rejected because the Applicant has not enabled the making and use of any attenuated RSV comprising any genetic alteration.

In the application, the Applicant has identified certain alterations of the RSV genome that may result in attenuated phenotypes. Additionally, the application suggests the use of multiple forms of scanning or random mutagenesis to identify genetic alterations that result in such attenuation. However, the Applicant has not identified all of the potential targets for genetic alteration that would result in attenuated forms of the virus. Further, not all genetic alterations are likely to result in attenuated virus. The art surrounding the alteration of proteins, which are encoded by viral genes, indicates both that such proteins are tolerant to alteration without loss of function, but that in each protein certain amino acids are tolerant to only a limited type, or to no, alteration without a loss of function. Bowie et al., Science 247: 1306-10, esp. page 1306 right column paragraphs 2 and 3. Bowie also teaches that the effect of any particular mutation is unpredictable absent teachings regarding the association of the residue(s) to be mutated with the protein's structure and function. Id. While the teachings of Bowie relate to proteins, these teachings would also relate to the modification of genes coding for proteins. Thus, the art indicates that mutation of any particular (one or more) nucleotides in the RSV genome may have no effect, may attenuate or increase the virus' virulence, or may prevent the rescue of a viable virus. Further, specific modifications to the regulatory domains of the viral genome could also be expected to achieve such varied results. Such expectations are supported by the teachings in the present application. See e.g., pages 61-63 (indicating that modifications to the viral gene encoding the L protein resulted in such varied results, some resulting in no change, some in attenuation, others in an increase in L protein function, and others in rendering a virus not

viable). The art therefore teaches that the art surrounding the claimed invention is therefore both largely unpredictable, and complex.

In contrast to these teachings, the present application provides very little in the specific identification of what nucleotides in the viral genome would be likely to achieve which of the potential effects. The Applicant has not provided sufficient detailed teachings of relating specific nucleotides of the genome to viral activities, or which of the nucleotides may be modified to achieve a viable virus with an attenuated phenotype, such that those in the are would be able to make and use attenuated RSV to the extent claimed. It is noted that the Applicant has provided screening methods to help make such determinations. It is also noted that the Applicant has provided information as to certain specific mutations that may be made to the genome that would result in attenuated phenotypes. However, the claims are not limited to such embodiments, and the information disclosed with relation to these specific mutations provides little guidance in comparison to the scope of what is being claimed.

In view of the large size of the viral genome and genetic alterations encompassed by the claims, an thus the number of potential mutations that may be made, the limited specific guidance, and the complexity and unpredictability in the art, the Applicant has not provided sufficient information to enable those in the art to make or use any attenuated RSV.

Claim Rejections - 35 USC § 102

13. **(Prior Rejections- Withdrawn)** Claims 49, 50, and 52 were rejected under 35 U.S.C. 102(a) as being anticipated by Crowe et al., Vaccine 12(8): 691-99, in light of the

teachings of Murphy (U.S. Patent). Claims 49-52 were rejected under 35 U.S.C. 102(a) as being anticipated by Crowe et al., Vaccine 12(9): 783-790, in light of the teachings of Murphy (U.S. Patent 5,993,824). The rejections are withdrawn.

14. **(New Rejection)** Claims 49, 52, 54, 57, 58, 59, 63, 64, and 68 are rejected under 35 U.S.C. 102(b) as being anticipated by Wright et al., Infection and Immunity 37: 397-400. These claims read on compositions comprising an attenuated RSV with a genetic alteration. While the claims include the limitation that the virus be "recombinant," this language appears to identify the virus by source, and does not appear to provide any structural feature by which to distinguish the claimed virus from viruses produced by other means.

Wright discloses a temperature sensitive variant of RSV which is described in the reference as having a mutation in the gene encoding the fusion protein of the virus. Abstract, page 399. The reference therefore anticipates the indicated claims.

15. **(New Rejection)** Claims 49, 51, 52, 54, 57, 58, 59, 62, 63, 64, 67, and 68 are rejected under 35 U.S.C. 102(b) as being anticipated by Wright et al., Journal of Pediatrics (of record in the IDS of March 2001). The claims have been described above. Although the reference does not teach where in the viral genome the mutations occur, the mutations are likely to be present in the functional and/or regulatory domains. The reference therefore anticipates the indicated claims.

16. **(New Rejection)** Claims 49, 51, 52, 54, 57, 58, 59, 62, 63, 64, 67, and 68 are rejected under 35 U.S.C. 102(b) as being anticipated by Crowe et al., Vaccine 11(14): 1395-404. These

claims have been identified above. Crowe teaches several attenuated RSV mutants. Although the reference does not teach where in the viral genome the mutations occur, the mutations are likely to be present in the functional and/or regulatory domains. The reference therefore anticipates the indicated claims.

Conclusion

17. No claims are allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Z. Lucas
Patent Examiner

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